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ELI LILLY AND COMPANY

By Kimberley K. Barker Date August 18, 2004

**PATENT APPLICATION**
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicants | : | Janet M. Hock et al. | |
| Serial No. | : | 09/647,278 | |
| Filed | : | September 26, 2000 | Group Art Unit: 1646 |
| For | : | Method of Increasing Bone Toughness and Stiffness and Reducing Fractures | Examiner: R. Li |
| Docket No. | : | X-11965 | |

**DECLARATION UNDER 37 C.F.R. 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hunter Heath III, M.D. declare that:

I received a bachelor's degree from Texas Technological College in 1964, and received the degree of Medical Doctor (M.D.) from Washington University in 1968. My views as expressed herein are based on more than 30 years' experience as a biomedical research scientist and clinician in the fields of bone & calcium metabolism, parathyroid hormone, and osteoporosis. I have published more than 160 peer-reviewed articles and book chapters during my career.

I have been employed by Eli Lilly and Company since 1996 in the following capacities:

- Distinguished Clinical Fellow: May 2004- Present
- Executive Director, U.S. Medical Division Jan. 2004 - Present
- Clinical Research Fellow: Jan 2004 – May 2004
- Senior Medical Director: Jan 2003 – Jan 2004
- Medical Director, U.S. Endocrinology: Mar 1996 – Jan 2003

I further declare that I have reviewed U.S. Patent 4,698,328 (hereinafter "Neer") and provide the following comments.

**Neer teaches co-administration of hPTH-(1-34) and a hydroxylated vitamin D compound**

This patent describes administering a broad dosage range of hPTH-(1-34) (100-700 units) in combination with either a hydroxylated form of vitamin D [preferably 1,25 $(OH)_2$ D], or with a calcium supplement for "increasing bone mass" in osteoporosis patients. Based on my experience and understanding of the field, it is my opinion that Neer teaches co-administration of hPTH-(1-34) and a hydroxylated vitamin D compound, and that those practicing in the field would not equate co-administering PTH and non-hydroxylated vitamin D with co-administering PTH and hydroxylated forms of vitamin D. Unhydroxylated vitamin D is an inactive parent compound that must be converted in the body to the active dihydroxylated form [*i.e.* 1,25 $(OH)_2$ D]. The teaching in the Neer patent is consistent with references published by Neer and others both before and after the patent, claiming that co-administering 1,25 $(OH)_2$ D, or another activated form of vitamin D, with hPTH-(1-34) was necessary because osteoporosis patients were defective in their ability to synthesize adequate amounts of 1,25 $(OH)_2$ D in response to hPTH-(1-34), even when ingesting adequate amounts of non-hydroxylated vitamin D (cf. Slovik et al., NEJM, 305, 372-374, 1981; Neer et al. Osteoporosis 1987 2, 829-835, Ed. Christainsen et al.). Thus, Neer teaches that patients had to be given 1,25 $(OH)_2$ D in order to bypass a defect in responsiveness to hPTH-(1-34).

**No rationale in Neer to choose Lilly's 20 ug/day dose for hPTH-(1-34)**

Neer teaches a broad dose range of 100-700 units with a preference for 400-500 units. Neer does not provide the corresponding dosage range in terms of a gravimetric quantity of peptide. As a clinician reading through the Neer patent there would have been no basis, instruction, or motivation for selecting Lilly's specific dose of 20 ug/day.

The vagaries of bioassays in general are well known, and are applicable with respect to potency assays for PTH. It is very difficult to know the mass of peptide corresponding to a given bioassay estimate, mainly because the precision of such assays is intrinsically poor. For a given amount of standard, the biopotency estimates using a given assay (e.g. chick hypercalcemia) may vary over a ten-fold range. Assay precision is even worse depending on the operator, the particular laboratory, the standard chosen, or the source

or diets of the animals used. Additionally, at the time of grant of the Neer patent, and continuing to the present, there was no International Reference Preparation standard for hPTH-(1-34) biopotency and no global standard assay method. In essence, there is no way to use the biopotency and dosing estimates in Neer to conclude that 20 ug hPTH-(1-34) per day would fall within the range of disclosed doses. In the past, investigators have relied on various PTH standards from animal sources or on internal "house-standards." In fact, only recently has the World Health Organization (WHO) initiated a project to establish an International Reference Preparation for hPTH-(1-34). With the high degree of imprecision and uncertainty in determining the potency of PTH samples, it is far more reliable and accurate to designate dosages of hPTH-(1-34) in terms of a gravimetric quantity of highly pure material.

**Lilly's 20 ug/day dose provided unexpected advantages**

The Neer patent showed an average increase in spinal (vertebral) bone density of about 20% in patients who were given hPTH-(1-34) at a dose of 500 units daily for more than a year, but no effect on bone mineral density outside the spine. Based on published data, one could not predict whether increased bone mineral density would decrease fracture risk in persons having osteoporosis. At no point in the patent does the applicant mention assessment of fracture risk, or make a claim for treatment-induced reduction in fracture risk. Indeed, the Neer study was far too small (8 patients) to permit assessment of fracture risk (required number of patients may exceed 1000). The Lilly studies unexpectedly discovered that fracture risk could be reduced at *both* spinal and nonspinal sites in patients treated with hPTH-(1-34).

Prior to Lilly's clinical trials there were no definitive dose-ranging studies with hPTH-(1-34) in the treatment of osteoporosis. Lilly's studies established a window of safety and efficacy of roughly 15 ug/day to 40 ug/day. Below this range there was inadequate effect; above 20 ug/day patients experienced an unacceptable frequency of undesirable side effects including headache, nausea, dizziness, and asymptomatic hypercalcemia and hypercalciuria.

Lilly's phase III trials showed that hPTH-(1-34) increased spinal BMD to a greater extent at 40 ug/day than at 20 ug/day. Specifically, the mean increase at 20 ug/day was about 10% while the increase at 40 ug/day was about 14%. Surprisingly, the fracture benefit was the same at both dose levels. Because an hPTH-(1-34) dose of 20 ug/day reduced

fracture risk equally to 40 ug/day, while associated with a much lower incidence of side effects, it was determined that 20 ug/day was preferable to 40 ug/day.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Hunter Heath III, M.D.

17 Aug 2004
Date